# A systematic review on tramadol toxicity in Iran - A distinct profile

**Yasna Rostam-Abadi[1], Masoumeh Amin-Esmaeili, Anousheh Safarcherati, Jaleh Gholami, Ramin Mojtabai, Mohammad Reza Ghadirzadeh, Hosein Rahimi, Afarin Rahimi-Movaghar**

[1:] MD, MPH student, Iranian National Center for Addiction Studies (INCAS), Tehran University of Medical Sciences, Tehran, Iran

## Introduction

Tramadol, an opioid analgesic used for both acute and chronic pain, was introduced as a safe pain medication in 2002 in the pharmaceutical market of Iran. Nevertheless, alarming reports of tramadol toxicity, tramadol induced seizures, and tramadol related mortality - incompatible with previous studies in other countries - resulted in the implementation of control policies since 2007 in Iran.

Tramadol is now a global public health issue, specifically in African and Middle-Eastern area. From less than 10 kg in 2010, global seizure of illegal tramadol reached 125 tons in 2017.

## Materials and methods

We aimed to systematically review all the relevant studies on tramadol toxicity and its health consequences in Iran.

Three international (Web of Science, Scopus, Medline) and one local (SID) databases were systematically searched up to June 2019 using a comprehensive search strategy.

Any study providing data on tramadol toxicity in the Iranian population was eligible.

Two independent reviewers screened all records for eligibility criteria and extracted relevant data from the included studies.

Data on tramadol toxicity and its health outcomes were presented without pooling and further analyses due to high heterogeneity among the studies.

## Results

From total 438 retrieved citations, 56 records investigated tramadol toxicity and its outcomes in Iran.

Twelve studies provided tramadol toxicity prevalence among all-cause or all-drug toxicities.

Tramadol toxicity ranged from 0.1% (in all emergency visits due to all-cause toxicities) to 39.0% (among all-drug toxicity admitted patients).

Among four studies on all drug-induced seizures or first seizures, tramadol was found to be the cause in 21.9% to 54.7% of cases.

In one study, tramadol constituted 1.5% of all-cause toxicities in pediatrics (aged under 12).

There were 33 studies evaluating all tramadol toxicities or tramadol induced seizures.

Patients tramadol toxicity were mostly under 30 years and were males.

The most common reason for toxicity were suicidal attempts (from 37.3% to 98.7%).

The mean dose resulting in toxicity was 363.2 to 3248 mg.

Previous tramadol abuse or dependence was reported by 3.8% to 66.4% of the patients.

Seizure prevalence ranged from 12.0% to 69.3%.

However, the most prevalent clinical manifestations were nausea, vomiting and altered mental status.

The mortality rate due to tramadol toxicity ranged from 0% to 10.0% among 25 studies reporting this measure. In the pediatric study, all patients survived.

## Conclusions

Tramadol toxicity remains a public health challenge in Iran in spite of control measures implemented in 2007. Forty-one out of 56 studies were implemented after 2007.

Most toxicity cases were young males attempting suicide.

Previous tramadol abuse or dependence varied notably across studies.

Tramadol related seizures were the most challenging complications; occurring in more than 30% of cases.

Due to the high potency of tramadol metabolites on both opioid and monoaminergic systems, ultra-metabolizers are more susceptible to toxicity.

The higher prevalence of ultra – metabolizers in African and Middle-Eastern regions may partly justify higher rates of tramadol toxicity and its health outcomes in these regions.

Tramadol related fatal cases had been reported in numerous studies; reaching up to 10% in one study.

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